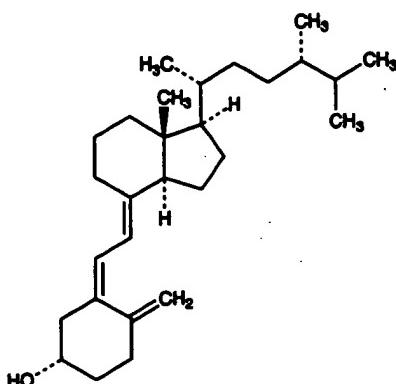


**EXHIBIT 1**

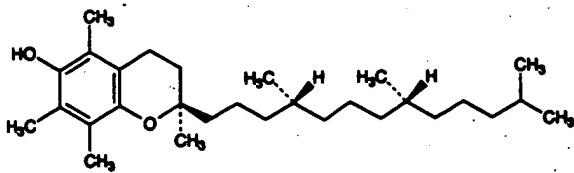
## Vitamin E

11.63%, O 4.01%. Prepd from 22:23-dihydroergosterol by irradiation with light of the magnesium arc: Windaus, Trautmann, *Z Physiol Chem.* 247, 185 (1937). Synthesis: P. J. Kocienski et al., *J. Chem. Soc., Perkin Trans. I* 1979, 1290.



Platelets from dil acetone, mp 96-98°. Originally given as mp 107-108°, see Windaus, Guntzel, *Ann.* 538, 122 (1939). Not  $[\alpha]_D^{25} +89.3^\circ$  ( $c = 0.47$  in acetone). uv max: 265 nm. Not precipitated by digitonin. Practically insol in water. Sol in the usual organic solvents except petr ether; slightly sol in vegetable oils.

**10159. Vitamin E. [2R-2R\*(4R\*,8R\*)]-3,4-Dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-ol; 2,5,7,8-tetramethyl-2-(4',8',12'-trimethyltridecyl)-6-chromanol;  $\alpha$ -tocopherol; (+)- $\alpha$ -tocopherol; 5,7,8-trimethyltocol; antisterility vitamin.  $C_{29}H_{50}O_2$ ; mol wt 430.71. C 80.87%, H 11.70%, O 7.43%. Found largely in plant materials. Present in highest concns (0.1-0.3%) in wheat germ, corn, sunflower seed, rapeseed, soybean oils, alfalfa and lettuce. Natural  $\alpha$ -tocopherol is usually found with  $\beta$ - and  $\gamma$ -tocopherols, q.q.v. Isolin from wheat germ: Evans et al., *J. Biol. Chem.* 113, 319 (1936). Structure: Fernholz, *J. Am. Chem. Soc.* 59, 1154 (1937); 60, 700 (1938). Synthesis: Karrer et al., *Helv. Chim. Acta* 21, 520, 820 (1938); Bergel et al., *J. Chem. Soc.* 1938, 1382; Smith et al., *Science* 88, 37 (1938); Smith, Sprung, *J. Am. Chem. Soc.* 65, 1276 (1943). Recent syntheses: N. Cohen et al., *Helv. Chim. Acta* 61, 837 (1978); eidem, *J. Am. Chem. Soc.* 101, 6710 (1979); R. Barnier, M. Schmid, *Helv. Chim. Acta* 62, 2384 (1979). Abs config of natural  $\alpha$ -tocopherol: Mayer et al., *ibid.* 46, 963 (1963). Stereoselective synthesis of the side chain: C. H. Heathcock, E. T. Jarvi, *Tetrahedron Letters* 23, 2825 (1982). Review of industrial processes: Rubel, *Vitamin E Manufacture* (Noyes Dev. Corp., Park Ridge, N.J., 1969). Reviews: *The Vitamins Vol. 5*, W. H. Sebrell, R. S. Harris, Eds. (Academic Press, New York, 1972) pp 165-317; J. M. Bieri, P. M. Farrell, *Vitam. Horm. (New York)* 34, 31-75 (1976). Book: *Ann. N.Y. Acad. Sci.* 393, entitled "Vitamin E: Biochemical, Hematological and Clinical Aspects", B. Lubin, L. J. Machlin, Eds. (1982) 506 pp. Review of medical uses: J. G. Bieri et al., *N. Engl. J. Med.* 308, 1063-1071 (1983).**



$[\alpha]_D^{25} -3.0^\circ$  (benzene);  $[\alpha]_D^{25} +0.32^\circ$  (alc).

Succinate, *Vitamin E acid succinate*. Prepn: Demole et al., *Helv. Chim. Acta* 22, 65 (1939); McArthur, Watson, *Can. Chem. Process Inds.* 23, 350 (1939); Baxter et al., *J. Am. Chem. Soc.* 65, 918 (1943). Needles from petr ether, mp 76-77°. uv max (ethanol): 286 nm ( $E_{1\text{cm}}^{25}$  38.5). Practically insol in water.

Nicotinate,  $C_{35}H_{53}NO_3$ , *Hijuven, Juvela Nicotinate, Renascin*.

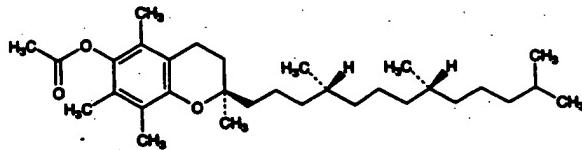
*dl*-Form, slightly viscous, pale yellow oil. Natural  $\alpha$ -tocopherol has been crystallized, mp 2.5°-3.5°.  $d_4^{25} 0.950$ ;

$b_{\text{P},1} 200-220^\circ$ ;  $n_D^{25} 1.5045$ . uv max: 294 nm ( $E_{1\text{cm}}^{25}$  71). Practically insol in water. Freely sol in oils, fats, acetone, alcohol, chloroform, ether, other fat solvents. Stable to heat and alkalies in the absence of oxygen. Not affected by acids up to 100°. Slowly oxidized by atm oxygen, rapidly by ferric and silver salts. Gradually darkens on exposure to light.

USE: As an antioxidant in vegetable oils and shortening. THERAP CAT: Treatment of vitamin E deficiency.

THERAP CAT (VET): Nutritional factor. Interrelationship with selenium. (Prevents muscle degeneration, also encephalomalaria and exudative diathesis.) Has been used to promote fertility.

**10160. Vitamin E Acetate. [2R\*(4R\*,8R\*)]-3,4-Dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-ol acetate; 2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-6-chromanol acetate;  $\alpha$ -tocopherol acetate;  $\alpha$ -tocopheryl acetate;  $C_{31}H_{52}O_3$ ; mol wt 472.75. C 78.76%, H 11.09%, O 10.15%. Prepn from *dl*- $\alpha$ -tocopherol and acetic anhydride: Surmatis, Weber, U.S. pat. 2,723,278 (1955 to Hoffmann-La Roche). Prepn of *d*- and *l*-forms: Robeson, Nelan, *J. Am. Chem. Soc.* 84, 3196 (1962). Stereoselective synthesis: K.-K. Chan et al., *J. Org. Chem.* 43, 3435 (1978). Total synthesis of all eight stereoisomers: N. Cohen et al., *Helv. Chim. Acta* 64, 1158 (1981). Comprehensive description: B. C. Rudy, B. Z. Senkowski, *Anal. Profiles Drug Subs.* 3, 111-126 (1974).**



*dl*-Form, *Detulin, Ephynal, Eprolin, Epsilan-M, Eusovit, E-Vimin, Evion, Juvela, OptoVit-E, Toco 500, Vitagutt*. Pale yellow, viscous liquid, mp -27.5°.  $d_4^{21.3} 0.9533$ .  $b_{\text{P},0.01} 184^\circ$ ;  $b_{\text{P},0.025} 194^\circ$ ;  $b_{\text{P},0.3} 224^\circ$ .  $n_D^{25} 1.4950-1.4972$ . uv max (cyclohexane): 285.5 nm. Practically insol in water. Freely sol in acetone, chloroform, ether. Less readily sol in alc. Unlike the free vitamins, the acetate is practically unaffected by the oxidizing influence of air, light, and ultraviolet light.

*d*-Form, [2R-[2R\*(4R\*,8R\*)]]-3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-ol acetate, *E-Vicotrat, Spondyvit, Tocopherex*. Crystals, mp 28°.  $[\alpha]_D^{25} +0.25^\circ$  ( $c = 10$  in chloroform);  $[\alpha]_D^{25} +3.2^\circ$  (in ethanol). *l*-Form, crystals, mp 23°.  $[\alpha]_D^{25} -2.0^\circ$  (in ethanol).

Note: The international unit of vitamin E is equal to one mg of standard *dl*- $\alpha$ -tocopherol acetate. The *d*-form is more active: 1 mg = 1.36 I.U. *l*- $\alpha$ -Tocopherol acetate has 42% of the activity of *d*- $\alpha$ -tocopherol acetate in the rat hemolysis test. Based on this activity a potency ratio of 1.4:1.0 for *d*- $\alpha$ -tocopherol acetate compared to *dl*- $\alpha$ -tocopherol acetate has been established.

THERAP CAT: Vitamin.

THERAP CAT (VET): Vitamin.

**10161. Vitamin K. General term referring to a group of naphthoquinone derivatives required for the bioactivation of proteins involved in hemostasis. The designation "K" was derived from the German "Koagulationsvitamin." Vitamin K compds are classified into 3 groups: *phylloquinone* ( $K_1$ ), q.v., found in green plants; *menaquinones* ( $K_2$ ), q.v., primarily produced by intestinal bacteria; and *menadione* ( $K_3$ ), q.v., and derivatives which are synthetic, lipid soluble compounds. Reduced *in vivo* to *dihydrotocopherol K* ( $KH_2$ ) which serves as a coenzyme in the conversion of glutamic acid residues to  $\gamma$ -carboxyglutamic acid (Gla), q.v., in the post-translational modification of blood coagulation factors II, VII, IX and X, q.q.v., and the anticoagulant proteins C and S. Other Gla-containing proteins, such as the bone matrix protein, osteocalcin, q.v., have been identified in a wide variety of tissues. This  $\gamma$ -carboxylation is accompanied by the oxidation of  $KH_2$  to *vitamin K epoxide* which is then recycled back to vitamin K. Discovery: H. Dam, *Biochem. Z.* 215, 475 (1929); 220, 158 (1930); *Nature* 135, 652 (1935). Historical survey: H. Dam, *Vit. Horm.* 24, 295-306 (1966). Menadione and phylloquinone are metabolized by animals**

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